

Mapping Human Toxicity and Disease Pathways in ToxCast™

ToxCast Data Analysis Summit

EPA, RTP

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ToxCast Pathway Approach

- **Bioinformatics**

database building and data analysis

- **Systems Biology**

mathematical modeling and reasoning to describe/infer biological phenomena

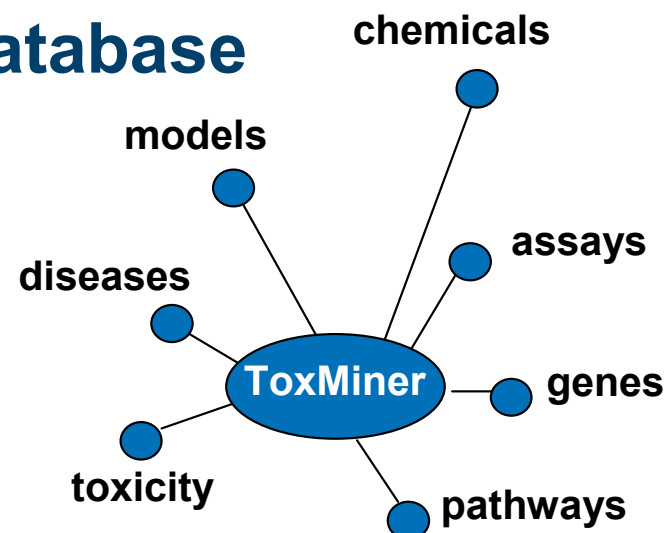
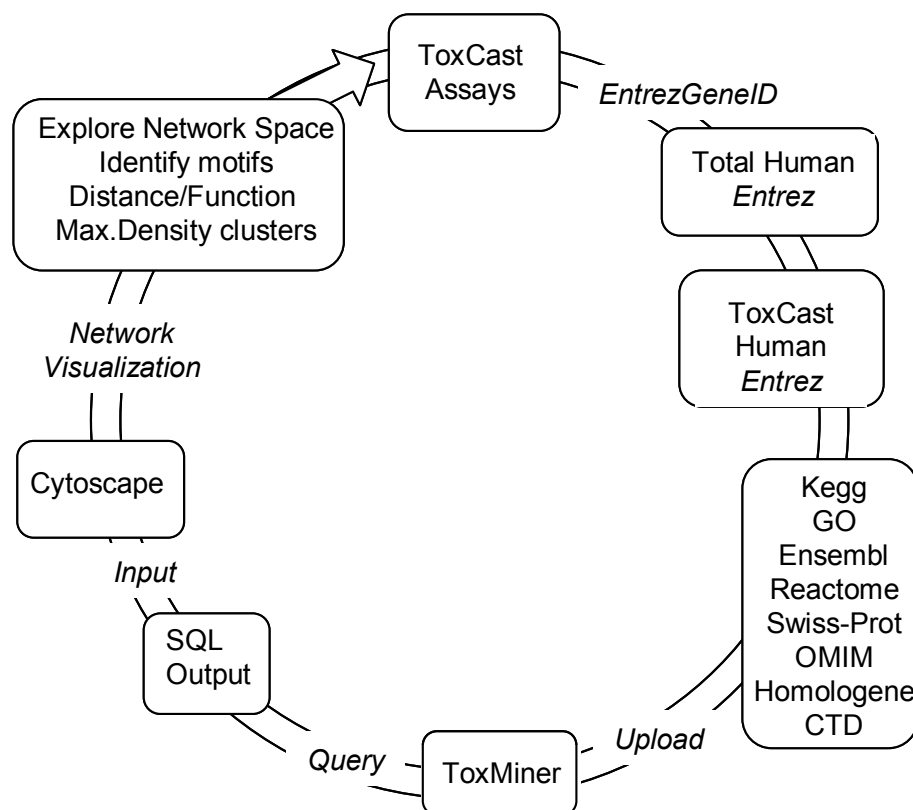
- **Computational Chemistry**

mathematical modeling of physical-chemical properties at the molecular level

- **Molecular Biology**

HTS technologies-genomics, proteomics, and metabolomics

ToxMiner Pathway Database



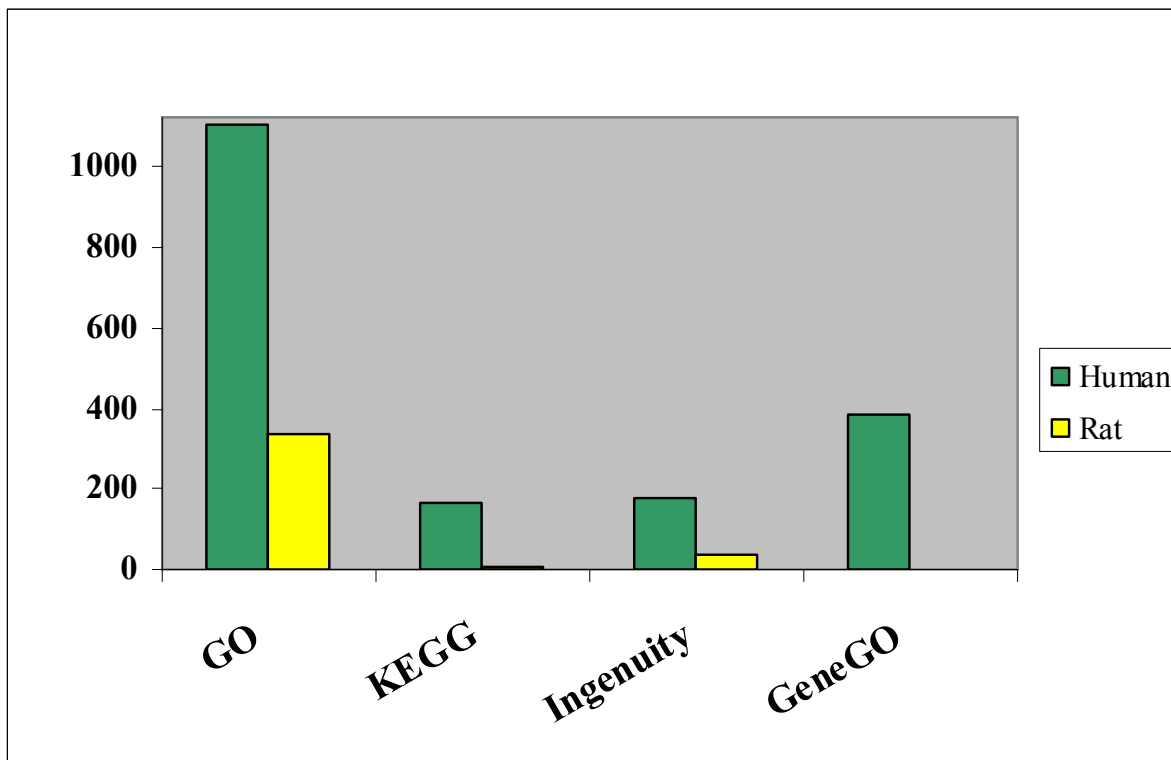
ACToR Aggregated Computational Toxicology Resource

The screenshot shows the ACToR web interface with the following details:

- Header:** ACToR: Aggregated Computational Toxicology Resource, U.S. ENVIRONMENTAL PROTECTION AGENCY
- Data Collection:** EPA CCL3
- Chemical Table:**

Chemical	SMILES	Chemical Name	EC50	EC10	EC01	EC001	EC0001	EC00001	EC000001	EC0000001	EC00000001
<chem>CC1=CC=CC=C1</chem>	1,2,3,4,5,6-hexachlorocyclohexane	1,2,3,4,5,6-hexachlorocyclohexane	100	10	1	0.1	0.01	0.001	0.0001	0.00001	0.000001
<chem>CC1=CC=CC=C1</chem>	1,2,3,4,5,6-hexachlorocyclohexane	1,2,3,4,5,6-hexachlorocyclohexane	100	10	1	0.1	0.01	0.001	0.0001	0.00001	0.000001

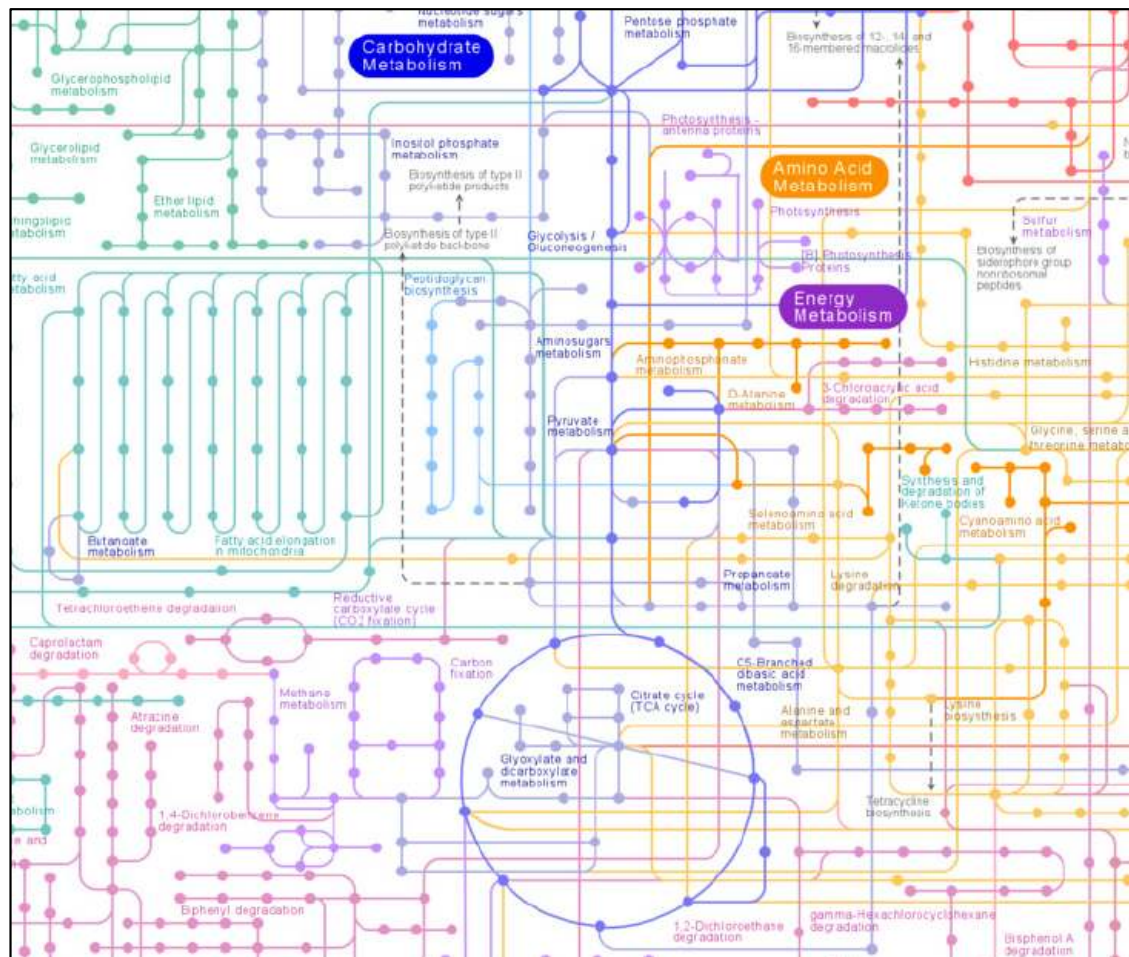
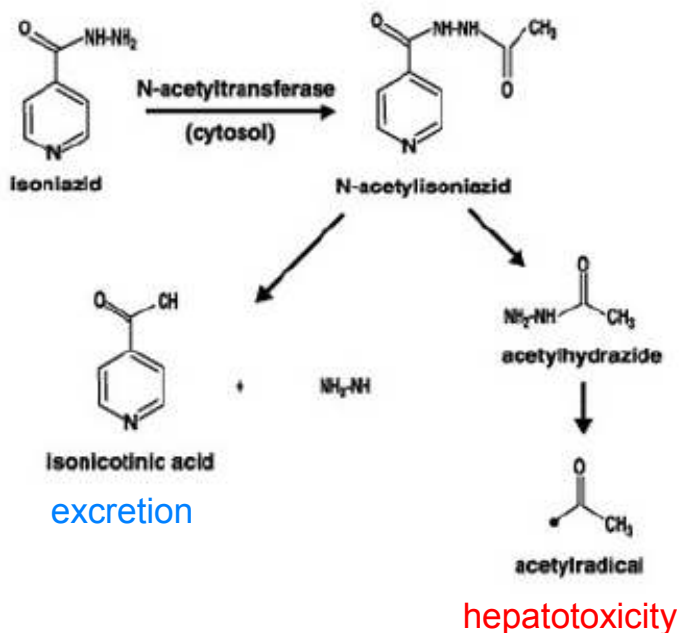
Pathways/Processes Identified by Analyses of ToxCast Data



	<i>Human</i>	<i>Rat</i>
GO	1104	336
KEGG	166	9
Ingenuity	180	39
GeneGO	385	-
Total Unique Entrez GeneID	236	51

What is a Pathway?

Pathway for Isoniazid Metabolism



adapted from KEGG Global Pathway Map (<http://www.genome.jp/kegg/>)

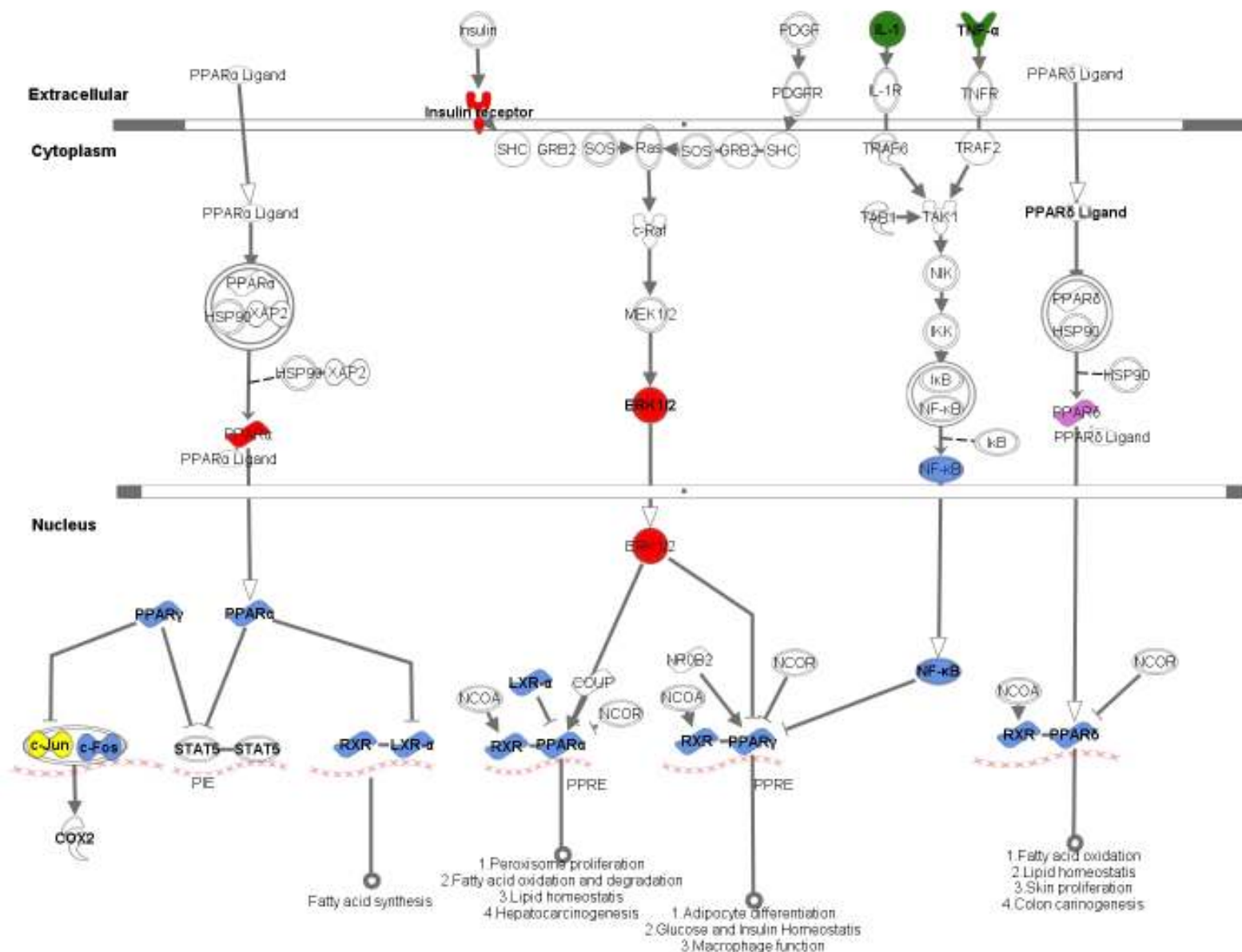
molecular pathway (muh-LEH-kyoo-ler...)

A series of actions among molecules in a cell that leads to a certain endpoint or cell function.

(taken from the NCI Dictionary of Cancer Terms)

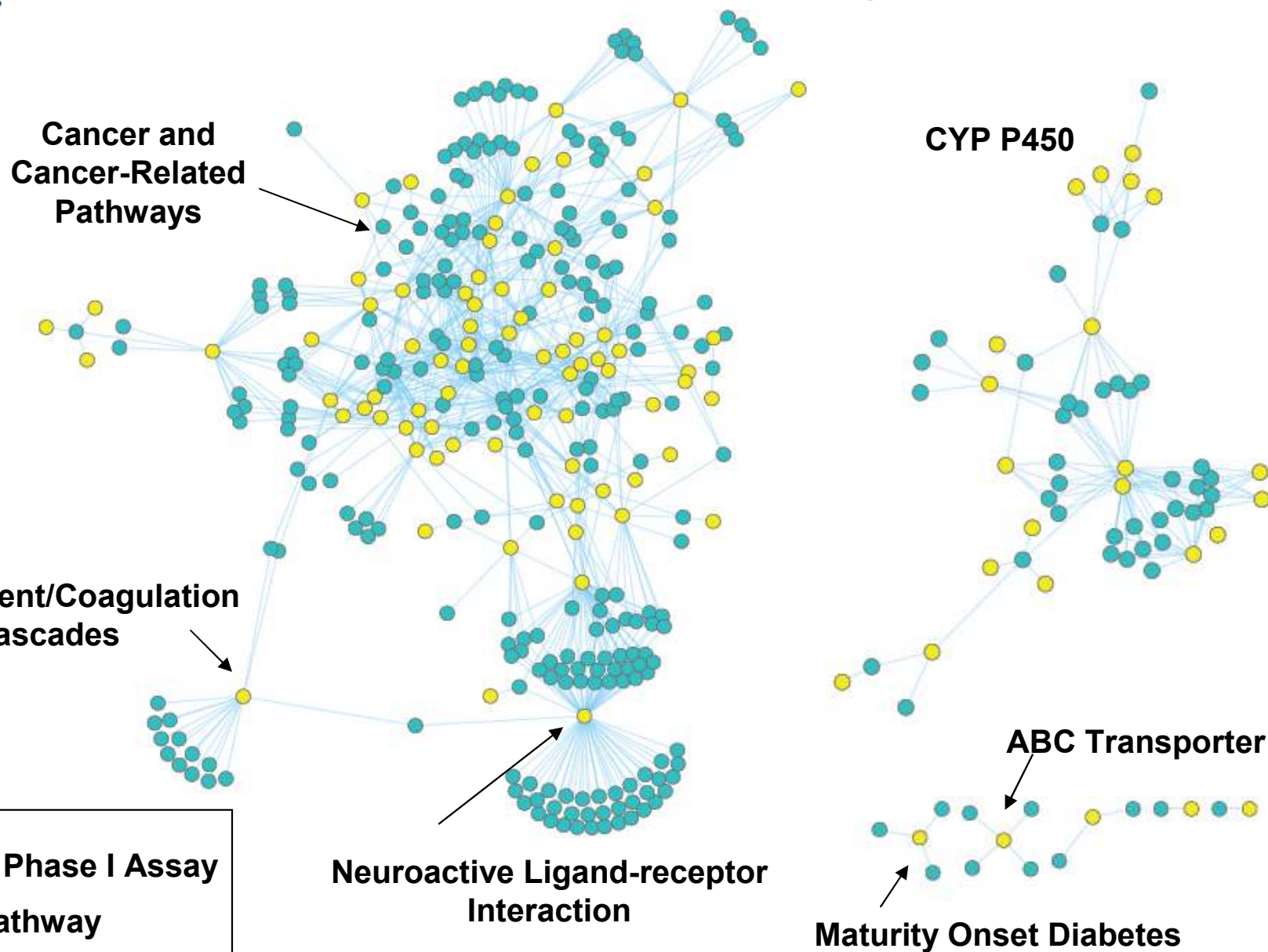
ToxCast Assay Targets in the PPAR Signaling Pathway

- Biologically Multiplexed Activity Profiling (BioMAP)
- Multiplex Transcription Reporter Assay
- Cell-based HTS Assays
- Cell-free HTS Assays
- High Content Cell Imaging Assays

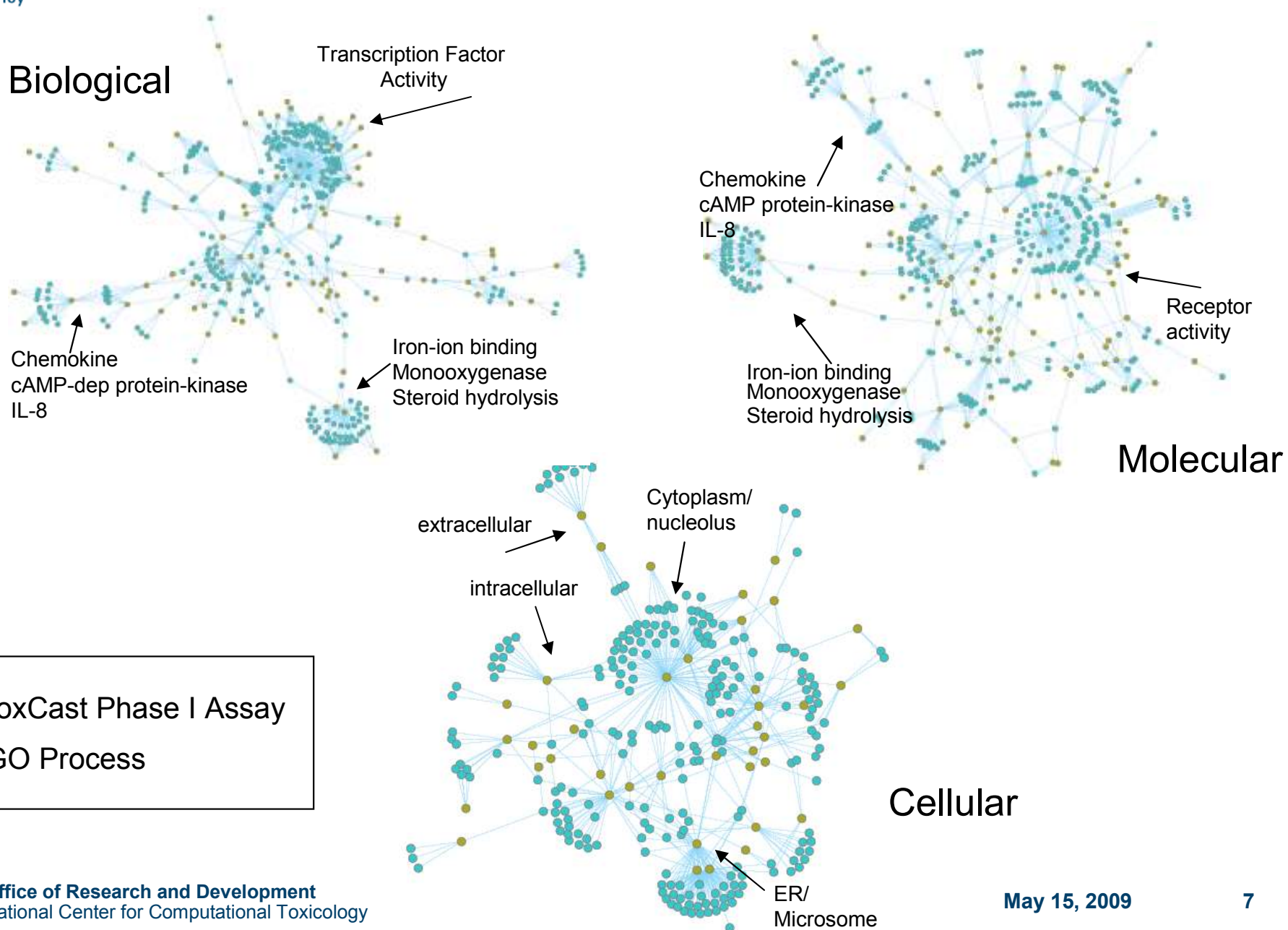


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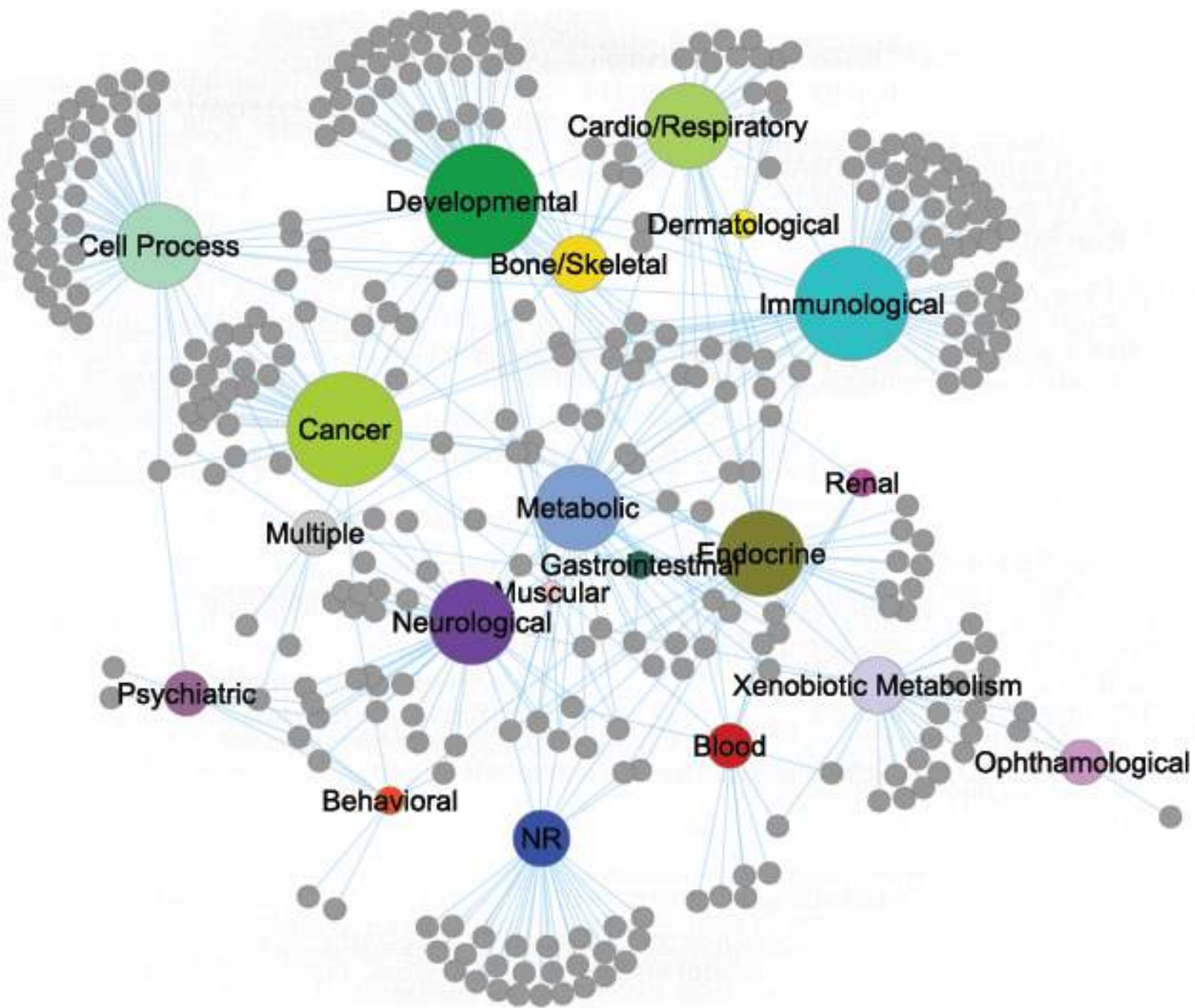
KEGG Pathways



Gene Ontology Processes



Disorder Classes Probed by ToxCast Assays



Genes Probed with ToxCast Assays by Disorder Class

Node Size

51-100

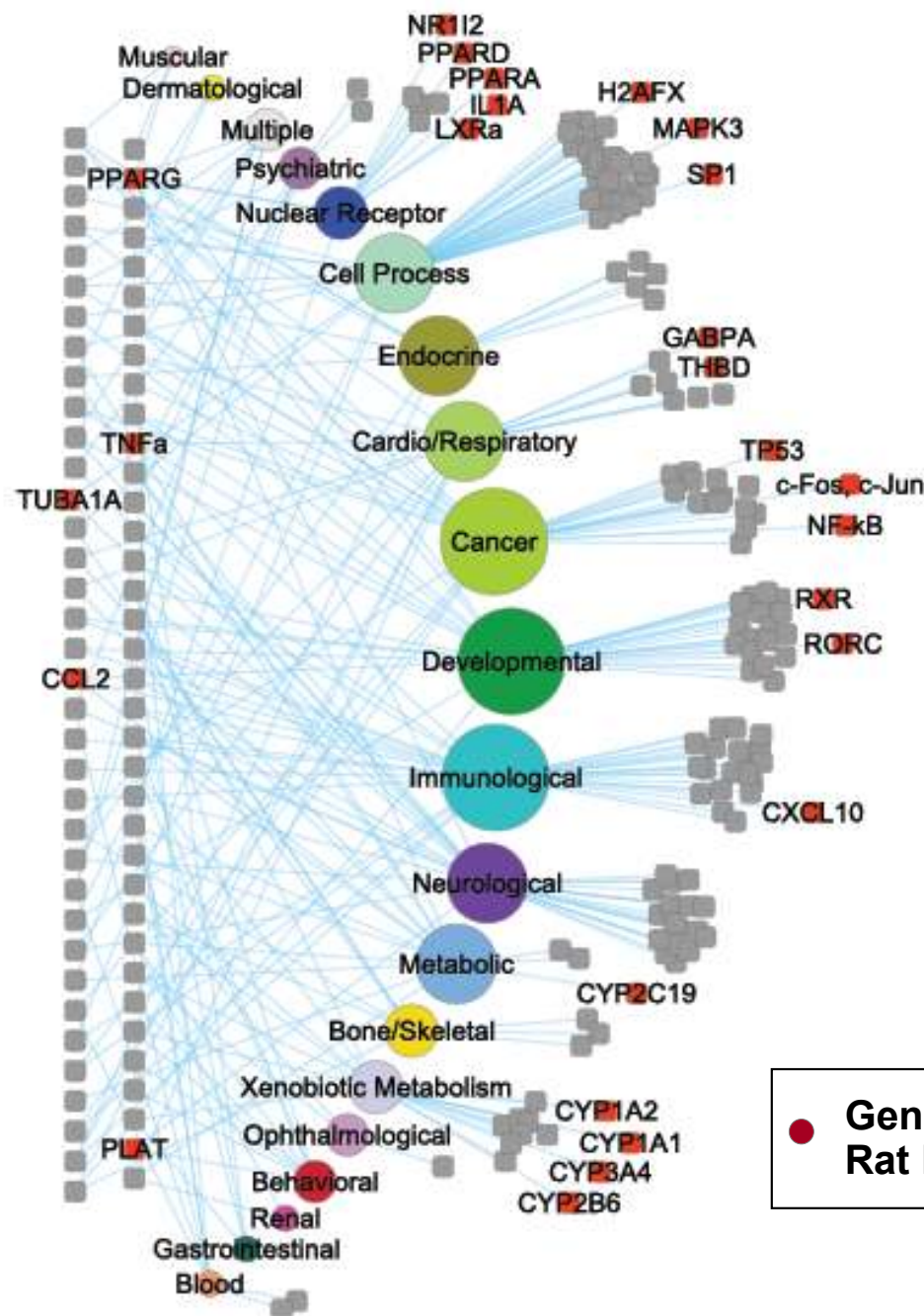
31-50

21-30

11-20

4-10

1



● Genetic Loci Associated with Rat Liver Proliferative Lesions

Future Directions

- Statistical Sound Approaches to Network Estimation
 - clustering coefficients
 - aggregate bootstrap
- Additional Data to Understand Toxicity Pathways
 - other HTS assays
 - direct testing of failed pharmaceuticals
 - *in vivo* data
 - modular networks/unsupervised methods

